



## ATTACHMENT B

### REMARKS

By this amendment, minor amendments to the claims have been made, namely, the formulas as utilized in the claims have now been entered directly into the claims as suggested by the Examiner. For reasons as set forth below and in the attached Declaration of Dr. Daniel C. Carter, Ph.D., the present claims are in compliance with Section 112, and in light of the fact that there were no prior art references cited, the present claims are clearly in condition for immediate allowance.

In the Official Action, the Examiner rejected Claims 1-7 under 35 U.S.C. § 112, second paragraph, on the basis that the structures of the claims should be presented in Claim 1. Without addressing the merits of this rejection, Applicants have adopted the suggestions of the Examiner by substituting the actual formulas in Claim 1 for their code numbers (with the exception of NCP023 which has been removed from the claims). The Examiner's rejection under Section 112, second paragraph is thus respectfully traversed.

In the Official Action, the Examiner rejected Claims 1-7 under 35 U.S.C. § 112, first paragraph, on the basis that the compounds of the claims were not described in such a way so that one skilled in the art would be able to make these compounds. For reasons as set forth below and in the attached Declaration of Dr. Daniel C. Carter,<sup>1</sup> this rejection is respectfully traversed.

In particular, as expressed in the attached Declaration, the present invention represents a significant advance in the field because it provides safer and more

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<sup>1</sup> The executed Declaration will follow shortly.

effective alternate drugs to the use of Warfarin (Figure 1) which has been on the market for over 50 years and is widely used in the prevention of thrombotic disease and stroke. One particular brand of warfarin is racemic sodium warfarin (also known as Coumadin), which is a product of Bristol Myers Squibb with current U.S. annual sales of approximately \$230 million, and the preparation of this warfarin is well documented and would be readily known by those skilled in the art. However, despite the large annual sales, and despite the fact that it is estimated to prevent twenty strokes per induced bleeding episode, warfarin is under-used because of the difficulty of controlling dosage and the fear of inducing bleeding. Coumadin's primary mode of action involves inhibiting microsomal vitamin K epoxide reductase and interfering with a number of vitamin K dependent blood clotting factors, including Factors II, VII, IX and X. Warfarin is thus a therapeutic with a low margin of safety and is considered 99% bound to plasma albumin *in vivo*, and it represents the precise reason for the development of the alternative compounds of the invention.

In accordance with the invention, our CADEX™ technology has allowed a closer picture of the structures of human serum albumin complexed with warfarin racemic mixtures and individual isomers, and has provided insight into the types of changes to warfarin that would have beneficial results. For example, changes that affect inhibition for vitamin K epoxide reductase should be avoided since it has been shown that only the coumarin ring is essential for the inhibition. Therefore, the compounds of the present invention have resulted from a focus on substitutions at the phenol ring on the other end of the warfarin molecule (Figure 1), and these changes can favorably affect the pharmacokinetics and safety of this important drug. These modifications were also

chosen because of the chemical availability of the coumarin ring (Figure 1) makes it easy for one skilled in the chemical arts to make the simple changes to the structure of warfarin to obtain the claimed compounds of the invention, and thus practical synthesis though standard and straightforward chemical reactions well known to those skilled in the art is all that is necessary to obtain these compounds.

As a result, it is clear that the presently claimed compounds can be readily be obtained by one of ordinary skill in the art, and that the Examiner's objection on the basis that one skilled in the art would not be able to make and use the invention is respectfully traversed and should be withdrawn.

Accordingly, in light of the present amendments and the arguments as set forth above, Applicant submits that the present application is in condition for allowance, and such action is earnestly solicited.

**END REMARKS**